

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P729 PC00	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/DK2004/000205	International filing date (day/month/year) 25/03/2004	(Earliest) Priority Date (day/month/year) 26/03/2003
Applicant Ostjysk innovation A/S		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 11 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).

3. ☒ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

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Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

The present invention relates to the use of compounds for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity, such as nephrotoxicity and ototoxicity, in particular where the cell toxicity is induced by a medical treatment. In a preferred embodiment the compounds have at least two nitrogen atoms, more preferably at least two amino groups. The compounds according to the invention are capable of blocking binding of cell toxic compounds to the megalin receptor, and thereby inhibiting uptake of the cell toxic compounds into cells. The invention further relates to novel compounds for use in said treatment, as well as a method for reducing the cell toxicity of cell toxic compounds, more particularly gentamicin.

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Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-37, 47-49 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

remark: diaminomethane and piperidine are not compounds according to the structural definition of formula 1

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-37,47-49 (partially)

Use of a compound of formulae I-VI for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity.

2. claims: 1-37,47-49 (partially) 38-41

Use of a moiety of gentamicin for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity.

3. claims: 47-49 (partially) 42-46

A compound of formula VII and uses thereof.

4. claims: 50-61

Method of reducing cell toxicity of a therapeutic agent comprising at least one cell toxic compound, said method comprising reducing the number of cationic groups from said at least one cell toxic compound.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/132 A61K31/16 A61K31/198 A61K31/4196 A61K31/445
A61K31/495 A61K31/53 A61K31/7008 A61P39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS, CHEM ABS Data, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 1 364 521 A (MERCK & CO INC) 21 August 1974 (1974-08-21) the whole document	1
P,X	WO 03/080103 A (MAX DELBRUECK CENTRUM ; WILLNOW THOMAS (DE)) 2 October 2003 (2003-10-02) abstract; claims 1,18,30,31 page 9, line 15 - page 10, line 5 ----- -/--	1,3,19, 29

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

24 August 2004

Date of mailing of the international search report

18. 11. 2004

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/053519 A (BURNS MARK ROBERT ; BANDUIR NAND (US); ORIDIGM CORP (US); GRAMINSKI GE) 11 July 2002 (2002-07-11) abstract page 11, line 30 - page 21, line 5 page 36, lines 11-20 page 9, line 21 - page 10, line 6 -----	1,2,4-6, 19-21, 28, 35-37, 47-49
X	WO 99/02145 A (DURANT GRAHAM J ; GWYNNE DAVID I (US); CAMBRIDGE NEUROSCIENCE INC (US)) 21 January 1999 (1999-01-21) the whole document -----	1-21,24, 28, 35-37, 47-49
X	EP 0 483 634 A (HOECHST ROUSSEL PHARMA) 6 May 1992 (1992-05-06) abstract page 3, line 12 - page 7, line 50; claims 1-14 -----	1-5, 7-13, 15-21, 24,28, 35,47-49
X	DE 100 53 506 A (MAX DELBRUECK CENTRUM) 2 May 2002 (2002-05-02) the whole document -----	1,2, 4-11, 18-21, 28, 35-37, 47-49
X	WO 89/05637 A (US BIOSCIENCE) 29 June 1989 (1989-06-29) abstract; examples 1-4 page 2, paragraphs 1,3 -----	1,4-6, 19,36, 37,47-49
X	US 6 177 434 B1 (KOPKE RICHARD D ET AL) 23 January 2001 (2001-01-23) abstract column 1, line 58 - column 2, line 47 -----	1-5, 7-13, 15-21, 24,28, 35,47-49
X	US 6 130 217 A (ARNOLD LEE DANIEL ET AL) 10 October 2000 (2000-10-10) column 1, line 50 - column 21, line 20 abstract -----	1,2,4, 7-13, 15-21, 28,35-37
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MILAM K M ET AL: "REDUCTION IN CIS DIAMMINEDICHLOROPLATINUM-II-INDUCED CYTOTOXICITY SISTER CHROMATID EXCHANGE AND DNA INTERSTRAND CROSS-LINKS IN 9L CELLS TREATED WITH THE POLYAMINE BIOSYNTHESIS INHIBITOR 2R 5R-6 HEPTYNE-2 5-DIAMINE" CANCER RESEARCH, vol. 49, no. 24 PART 1, 1989, pages 6945-6948, XP008033957 ISSN: 0008-5472 abstract page 6946, column 2 - page 6947, column 2, paragraph 3; figure 1; tables 1,2	1,4-6, 19-21, 28,29, 32,33, 35-37, 47-49
X	HEYS, STEVEN D. ET AL: "Potentiation of the response to chemotherapy in patients with breast cancer by dietary supplementation with L-arginine: results of a randomized controlled trial" INTERNATIONAL JOURNAL OF ONCOLOGY, 12(1), 221-225 CODEN: IJONES; ISSN: 1019-6439, 1998, XP008033963 abstract	1,4-6, 17, 19-21, 28,35, 36,47-49
X	TOMIDA A ET AL: "NOVEL MECHANISM OF N SOLANESYL-N N'-BIS-3 4-DIMETHOXYBENZYLETHYLENEDI AMINE IN POTENTIATION OF ANTITUMOR DRUG ACTION ON MULTIDRUG-RESISTANCE AND SENSITIVE CHINESE HAMSTER CELLS" JAPANESE JOURNAL OF CANCER RESEARCH, vol. 82, no. 1, 1991, pages 127-133, XP008033945 ISSN: 0910-5050 abstract	1,2,4,5, 15-17, 19-21, 28, 35-37, 47-49
X	WO 01/12607 A (DARRO FRANCIS ; KISS ROBERT (BE); GUILLAUMET GERALD (FR); JOSEPH BENOI) 22 February 2001 (2001-02-22) abstract page 2, line 27 - page 4, line 28 page 10, line 12 - page 12, line 4; examples 32,33,35,37,38,58,59,61-66,73 page 112, line 4 - page 178, line 20	1,2,4, 7-13,15, 17-21, 28, 35-37, 47-49
X	FAN DOMINIC ET AL: "Reversal of multidrug resistance in murine fibrosarcoma cells by thioxanthene flupentixol" INVESTIGATIONAL NEW DRUGS, vol. 12, no. 3, 1994, pages 185-195, XP008033946 abstract	1,2,4,5, 15-17, 19-21, 28, 35-37, 47-49
3	-/--	

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LIN P K T ET AL: "The synthesis and in vitro cytotoxic studies of novel bis-naphthalimidopropyl polyamine derivatives" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 14, 17 July 2000 (2000-07-17), pages 1609-1612, XP004209715 ISSN: 0960-894X the whole document	1-37
A	EDWARDS M L ET AL: "POLYAMINE ANALOGUES WITH ANTITUMOR ACTIVITY. POLYAMINE ANALOGUES WITH ANTITUMOR ACTIVITY" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, US, vol. 33, no. 5, 1 May 1990 (1990-05-01), pages 1369-1375, XP000604648 ISSN: 0022-2623 the whole document	1-37
X	WIEBKIN P ET AL: "INHIBITION OF METABOLISM MEDIATED CYTO TOXICITY BY 1 1 DI SUBSTITUTED HYDRAZINES IN MOUSE MASTO CYTOMA LINE P-815 CELLS" BIOCHEMICAL PHARMACOLOGY, vol. 31, no. 18, 1982, pages 2921-2928, XP001199476 ISSN: 0006-2952 the whole document	1
X	KONDRATOV R V ET AL: "Small molecules that dramatically alter multidrug resistance phenotype by modulating the substrate specificity of P-glycoprotein" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, US, vol. 98, no. 24, 20 November 2001 (2001-11-20), pages 14078-14083, XP002259950 ISSN: 0027-8424 the whole document	1-5, 7-13, 15-22, 28, 35-37, 47-49
X,P	WO 03/066572 A (OCHSNER CYNTHIA E ; COPP RICHARD R (US); FAHL KATHLEEN L (US); FAHL WI) 14 August 2003 (2003-08-14) the whole document	1,2,4-6, 19-21, 35-37, 47-49

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
GB 1364521	A	21-08-1974	DE 2234804 A1	25-01-1973
			FR 2146295 A1	02-03-1973
			NL 7209320 A	18-01-1973
WO 03080103	A	02-10-2003	WO 03080103 A1	02-10-2003
WO 02053519	A	11-07-2002	CA 2433807 A1	11-07-2002
			EP 1373185 A2	02-01-2004
			JP 2004529082 T	24-09-2004
			WO 02053519 A2	11-07-2002
			US 2003187276 A1	02-10-2003
WO 9902145	A	21-01-1999	AU 8278498 A	08-02-1999
			WO 9902145 A1	21-01-1999
EP 0483634	A	06-05-1992	US 5039666 A	13-08-1991
			AT 133072 T	15-02-1996
			AU 640056 B2	12-08-1993
			AU 8680291 A	07-05-1992
			CA 2054471 A1	01-05-1992
			DE 69116503 D1	29-02-1996
			DE 69116503 T2	20-06-1996
			DK 483634 T3	20-05-1996
			EP 0483634 A2	06-05-1992
			ES 2083500 T3	16-04-1996
			GR 3018824 T3	30-04-1996
			HU 60136 A2	28-08-1992
			IE 913775 A1	22-05-1992
			IL 99874 A	31-08-1995
			JP 3003333 B2	24-01-2000
			JP 4282315 A	07-10-1992
			KR 139199 B1	15-05-1998
			PT 99358 A ,B	30-09-1992
			ZA 9108592 A	29-07-1992
DE 10053506	A	02-05-2002	DE 10053506 A1	02-05-2002
WO 8905637	A	29-06-1989	AT 102826 T	15-04-1994
			AU 629533 B2	08-10-1992
			AU 2922389 A	19-07-1989
			CA 1328619 C	19-04-1994
			DE 3888541 D1	21-04-1994
			DE 3888541 T2	23-06-1994
			EP 0391971 A1	17-10-1990
			JP 2951344 B2	20-09-1999
			JP 3503162 T	18-07-1991
			US 5292497 A	08-03-1994
			WO 8905637 A1	29-06-1989
US 6177434	B1	23-01-2001	US 2001007871 A1	12-07-2001
US 6130217	A	10-10-2000	NONE	
WO 0112607	A	22-02-2001	FR 2797444 A1	16-02-2001
			AU 7012200 A	13-03-2001
			CA 2381968 A1	22-02-2001
			EP 1202971 A2	08-05-2002
			WO 0112607 A2	22-02-2001

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0112607	A	US 6645983 B1	11-11-2003
WO 03066572	A	14-08-2003	
		CA 2475349 A1	14-08-2003
		WO 03066572 A1	14-08-2003
		US 2003185778 A1	02-10-2003